REMARKS

The finality of the restriction requirement has been noted.

Claims 1-2, 4-29, 32-34 and 36-72 are rejected under 35 U.S.C.§112, first paragraph.

Reconsideration is requested.

The term "micromatrix particles" was used in original claim 1 as well as in the specification at page 15, lines 15-30. The text of the specification explains the structure of the micro-matrix particles which are also illustrated in the specific examples. Figs 4(a) and 4(b) also provide diagrams to illustrate what is meant by micro-particles. Based on this detailed disclosure of how to make and use the microparticles, it is requested that this ground of rejection be withdrawn.

Claims 1, 4-5, 8-11, 14-29 and 32 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis).

Reconsideration is requested.

The Examiner has taken the position that the word "comprising" does not exclude the presence of talc. In response to this objection, claim 1 has been amended to point out that the formulation is one "consisting essentially of" the recited materials. In addition, the term "consisting" been substituted for the term "comprises" with regard to the reference to the inner and outer portion of the dosage form. The term "hydrophobic release controlling agent" has been introduced into the claims based on the specification at page 15, line 30. In addition, the substance of claim 2 has been incorporated

into claim 1 so that claim 1 now recites that the inner portion is covered by the outer portion from all sides except that the top surface remains uncovered.

Glassman discloses double layer tablets wherein the outer layer preferably contains pure active ingredient, This inner portion is separated immediately on contact with GI fluid to provide super fast release of drug and the second tightly compressed layer disintegrates slowly for sustained / delayed action. Glassman teaches that quicker dissolution of the top layer may be achieved, by adding a bicarbonate salt to the top layer. Moreover, both the layers are essentially connected by a middle layer (Fig 2, layer 18) of talc or corn starch for cementing and said layer may also contain an effervescent combination for rapid release of the outer layer.

The objective of this invention is to reduce the latent period particularly for slow acting compositions where immediate therapeutic action followed by sustained effect is essential in the treatment of Asthma, Angina etc.

Claims 1 and 33 have been amended to recite that the inner portion is covered by the outer portion from all the sides except a top surface that remains uncovered. This language is found in original claim 2 and is not new matter and is not disclosed or suggested by Glassman.

Glassman discloses a sustained / delayed release action that is obtained using enteric coating and does not teach the use of hydrophobic release controlling agents. In addition this prior art reference clearly mentions the use

of single drug formulation having immediate and sustained release profiles to achieve instant action and sustained action. It does not describe a tablet where a structure is embedded in a tablet where only the top surface remains uncovered and for this reason, does not teach the controlled release dosage formulation that is defined by amended claim 1. use of combination of drug using the said formulation.

Paradissis only discloses an extended release pharmaceutical composition particularly adapted to approach **zero** order drug release over a period of 12 - 24 hours. The release of the drug in the present invention is controlled through diffusion. It discloses mixture of an immediate release particle containing a core of drug, inert spherical substrate particles and binder, **coated with talc**. The talc, which is essentially required, is employed to prevent the drug layer from interfering with film formation on the particles and to **prevent drug migration during storage (col. 6 line 5-12)**. The formulation essentially comprises particles of -10 + 60 mesh of particle size, to achieve the desired release of the drug (col. 3 line 30-33 and claim 1).

It has been found by the inventors of the present application that when the difference between the dosage strengths of two components is very high and particularly in the case of high solubility drugs, it is difficult to formulate a dosage form that will provide a sustained release profile. The present invention discloses a combination of a high dose-high solubility active ingredient of a controlled release dosage form in

combination with a low dose active drug as immediate release component. This significantly reduces the amount of inactive components and thereby reduces the size of the dosage form for ease of swallowing and economy.

There is no suggestion or teaching in either Glassman or Paradissis that would lead a skilled artisan to the claimed invention. Neither reference suggests a inlaid tablet structure where only one of six sides of an discrete section are exposed to the outer surface of the tablet. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1-2 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis)and Webb et al. (Webb)

Reconsideratrion is requested.

The Glassman and Paradissis references have been distinguished from claim 1 above. The Examiner noted at pages 11 and 17 of the Office Action that the applicant had not provided any additional arguments about the Webb patent. The Examiner is requested to consider pages 25-26 of the Amendment filed March 12, 2007 where detailed comments were made on the teachings of the Webb patent.
Webb discloses a multiple compressed tablet having discrete zones which are made from a formulation (A) having sustained release profile containing a active ingredient (particularly a sympathomimetic agent) using water soluble non-ionic cellulose ethers in an amount from about 18% to 50 % by wt of formulation A, one or more anionic surfactants in an amount from about 2% to 20 % by wt of formulation A with other pharmaceutically acceptable excipients and formulation (B) having immediate release

profile containing drug, calcium carbonate in an amount from about 0.5% to 25% by wt of formulation B, nonionic surfactants in an amount from about 1% to 10 % by wt of formulation B and both can be compressed by different processes such as layering, inlay etc.

Thus, this invention particularly teaches formulation for sympathomimetic agents and **essentially requires surfactants and calcium carbonate**. It does not teach a tablet having a high dose-high solubility active ingredient and a low dose active ingredient as an immediate release active ingredient. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1, 6-7 and 12-13 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis)and Lerner et al. (Lerner)

Reconsideration is requested.

The Glassman and Paradissis references have been distinguished from claim 1 above. The Examiner noted at pages 13 and 19 of the Office Action that the applicant had not provided any additional arguments about the Lerner patent. The Examiner is requested to consider page 29 of the Amendment filed March 12, 2007 where detailed comments were made on the teachings of the Lerner patent.

Lerner describes a gastrointestinal drug delivery systems for delivery of enterally administered compositions to specific locations along the GI tract. In particular, the colon is targeted as a release site. The Lerner invention is directed to a composition comprising a core and coating wherein the core contains drug with carrier material, which preferably swells in contact with GI fluid. Lerner teaches that the formulation operates by allowing the slow introduction of fluid into the device, which swells the

particulate matter and the particles eventually form channels from the outer part of the device to the core containing the drug and the drug can than be released from the channels. This formulation controls the release of the drug at a particular site of absorption based on the various parameters such as thickness of the outer coating (essentially contains rate controlling agents), the amount of particulate embedded in the coating, the type of particulate embedded in the coating, the particle size distribution of the particulate embedded in the coating and the core carrier. Thus Lerner is limited to the disclosure of a delivery device for site specific delivery of drug and having drug release through osmotic channels and the release is controlled by a combination of hydrophilic particulate and hydrophobic component (col. 20 line 36-col. 21 line 47). This patent not teach the dual retard technique for combination of immediate release and sustained release formulations without the use of hydrophilic particulate matter. For these reasons, this combination of references fails to make claims 1, 6-7 and 12-13 obvious and it is requested that this ground of rejection be withdrawn.

Claims 33,36-37, 40-60, 62-65, 68-69 and 71-72 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis)and Timmins.

The Glassman and Paradissis have been distinguished from claim 1 above and since they fail to disclose the combination of a low dose drug and a highly soluble drug particularly inlaid tablet, they can not disclose a low dose antidiabetic drug and a highly soluble anti diabetic drug as claimed in claim 33. The Examiner

noted at pages 13 and 19 of the Office Action that the applicant had not provided any additional arguments about the Timmins patent. The Examiner's is requested to consider page 28 of the Amendment filed March 12, 2007 where detailed comments were made on the teachings of the Timmins patent.

The Timmins patent discloses biphasic controlled release system for a highly soluble active ingredient, particularly metformin, either alone or in combination, which contains an inner and outer phase. Timmins teaches that highly soluble drugs having a higher dosage strength with a narrow absorption window will not exhibit a controlled release profile in a matrix or multiparticulate controlled release system. These release formulations invariably compromise the availability of drugs such as metformin. It further teaches that bioavailability with an extended release dosage form of metformin can only be achieved with an extended residence time in upper GI tract. Invention also discloses that prior art techniques for gastroretentive system such as floating, bioadhesive and swelling are not very suitable for very highly water soluble drugs. Thus, Timmins teaches a delivery system which achieves extended gastric residence by virtue of size but will degrade *in vivo* so as not to cause obstruction. This system also includes an inner solid particulate phase formed of substantially uniform granules of active drug with hydrophilic / hydrophobic/ material and an outer continuous phase including a rate controlling material, which the above granules are dispersed and embedded. Therefore Timmins teaches away all dosage forms other than gastroretentive by virtue of size for highly soluble active ingredient like metformin and further it also does not

teach any dual retard technique for a sustained release formulation having an immediate release component. For these reasons, it is requested that this ground of rejection be withdrawn.

None of the prior art teaches such a techniques for high dose high solubility drugs, which reduces burst effect and also reduces the size of the dosage form. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 33-34 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis)and Timmins and Webb.

Reconsideration is requested.

The cited references have been distinguished above from the claimed invention. The combination of both Webb and Timmins does not make the claimed subject matter of claims 33 and 34 obvious for the reasons set forth above. As amended, claim 33 recites that the immediate release dosage form has only one surface exposed in the final dosage form and the provision of an immediate release form of a highly active drug in this type of a structure is not made obvious by this combination of references. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 33, 36-39 and 44-45 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis)and Timmins and further in view of Lerner.

Reconsideration is requested.

The cited references have been distinguished above from the claimed invention. The combination of both Timmins and Lerner fail to make the claimed subject matter of claims

33, 36-39 and 44-45 obvious for the reasons set forth above. There is no disclosure which acts to direct one skilled in the art to a priori combine the diverse teaching of the cited references without the benefit of the applicants specification. Lerner does not have an exposed inlay and for this reason, there is no reason to consider this ground of rejection as being applicable to the amended claims. For these reasons, it is requested that this ground of rejection be withdrawn.

The present specification in Figs, 6 and 7 shows the controlled release of high dose, high solubility active agents identified as Nos. 11 & 12 and Nos. 15 & 16 which correspond to Example 1 & 2. The test results were obtained from a dosage form that was prepared using the dual retard technique as described in the present invention. The release of high dose, high solubility active agent in Nos.13 & 14 and 17 & 18 in accordance with examples 3 & 4 from dosage forms prepared without using the dual retard release technique. The total quantity of the hydrophobic release controlling agent is the same in all the dosage forms in spite of that the figures clearly shows that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high dose, high solubility active ingredient for prolonged period. These data are evidence of the unobviousness of the present invention as defined by the amended claims.

An early and favorable action is earnestly solicited.

Respectfully submitted,

James V. Costigan
Registration No. 25,669

Hedman & Costigan, P.C.,
1185 Avenue of the Americas
New York, NY 10036
(212) 302-8989